# Pediatric Formulation of ARVs
# Summary of April 28, 2005 Workshop

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www.hivforum.org

**Forum for Collaborative HIV Research**

**School of Public Health & Health Services**

**The George Washington University**

The Forum for Collaborative HIV Research is a public/private partnership including government agencies, the pharmaceutical industry, HIV researchers and clinicians, and the HIV patient advocacy community.

Our mission is to facilitate and enhance HIV research.

# Pediatric Project Steering Committee

David Burger - Radbound University Medical Centre Nijmegen

Ben Cheng - FCHR

Polly Clayden - HIV I-Base

Siobhan Crowley - WHO

Courtney Fletcher - University of Colorado

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Richard Hoetelmans - Tibotec

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Lynne Mofenson - NICHD

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Jeff Safrit - Elizabeth Glaser Pediatric AIDS Foundation

Steve Spector - UC San Diego

John Gerber – U Colorado

# April 27 Workshop (Co-funded by the EGPAF)

- Regulatory Agencies: Canada, Europe, South Africa, US
- Industry: Abbott, Apotex, BMS, Cipla, Gilead,GSK, Merck, Pfizer, Schering-Plough,Tibotec
- HIV i-Base, MSF, TAC
- EGPAF, IAS, MRC, NIH (NICHD, NIAID), WHO
- PACTG, PENTA
- Clinical pharmacologists, clinicians, researchers

# Meeting Objectives

- To identify the issues pertinent to pediatric formulations and treatment of HIV/AIDS in children
- To identify barriers to development of pediatric formulations
- To identify research questions that need to be addressed to develop guidelines and dosing regimen
- To identify the role of the various agencies and organizations in moving this field forward
- This workshop a first in a series of discussions

# Pediatric Formulations

- Liquid formulations needed for very small infants
  - Liquid formulations not choice for most pediatric settings
  - Weight, stability, transportation
- Solid Formulations
  - Smaller dosing units
  - Scored tablets
  - Powders
  - Adult tablets
    - Breaking, crushing
    - Effect of crushing on bioavailability

# Key Barriers to Pediatric HIV ART Treatment -

**Lack of:**

- **Advocacy and attention to children**
- **Trained pediatric health care professionals, with expertise or experience in treatment of HIV**
- **Affordable diagnostics**
- **Affordable available ARV for ped use**
- **Data for production and demand forecasting**

S. Crowley, WHO

## WHO/UNICEF Technical Consultation: Improving Access To Appropriate Paediatric ARV Formulations

**Nov 3 -4, 2004**

1. Principles and practice for best use of currently available ARVs
2. Principles and priorities for design and development of modified/new ped ARVs
3. Demand forecasting & programme indicators for M & E of ped HIV care and ART.
4. Gaps, obstacles and priority operational research needs.

Experts form North & South, pharmacologists, regulators and product dev $^{mt}$ experts

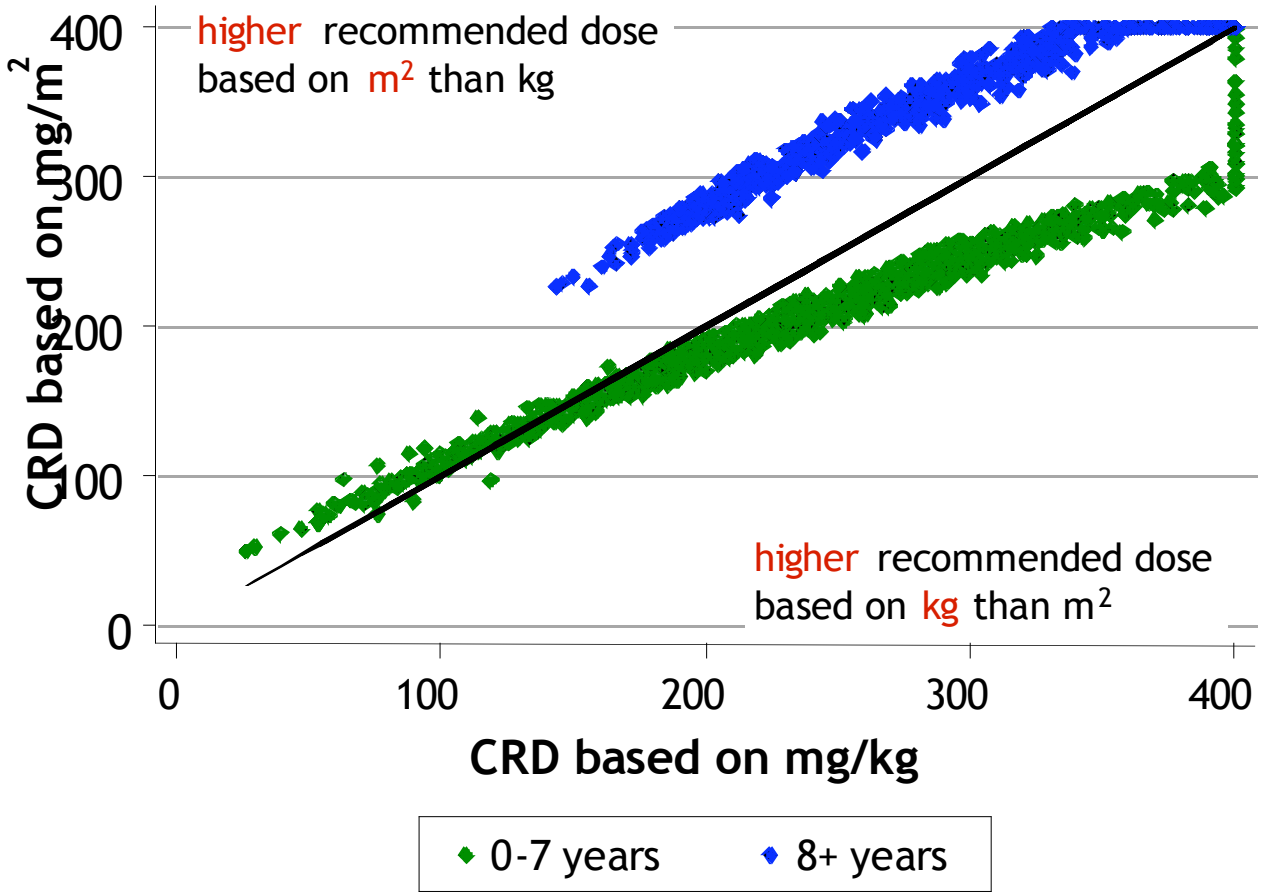
# Dose calculations in children

- By body weight
  - Incl
- By su
  - drug
  - PK
  - requ
  - sub
    - 
    - 
- In 19
  (UKC
  base

# Dose recommendations

## Impact of alternative calculation methods

Nevirapine : CRD based on kg and m $^2$ dosing



# Reasons for underdosing

Review of 53 pharmacy records / notes at one centre

- failure to increase dose as child grew / rounding down of doses 56%
- formulation limitations 33%
- clinical indication / drug interaction ~5%

♉ 'system failures'

- e.g. children missing clinic appointments
- lack of pharmacy checks

(addressed since – multi -disciplinary meeting prescribing)

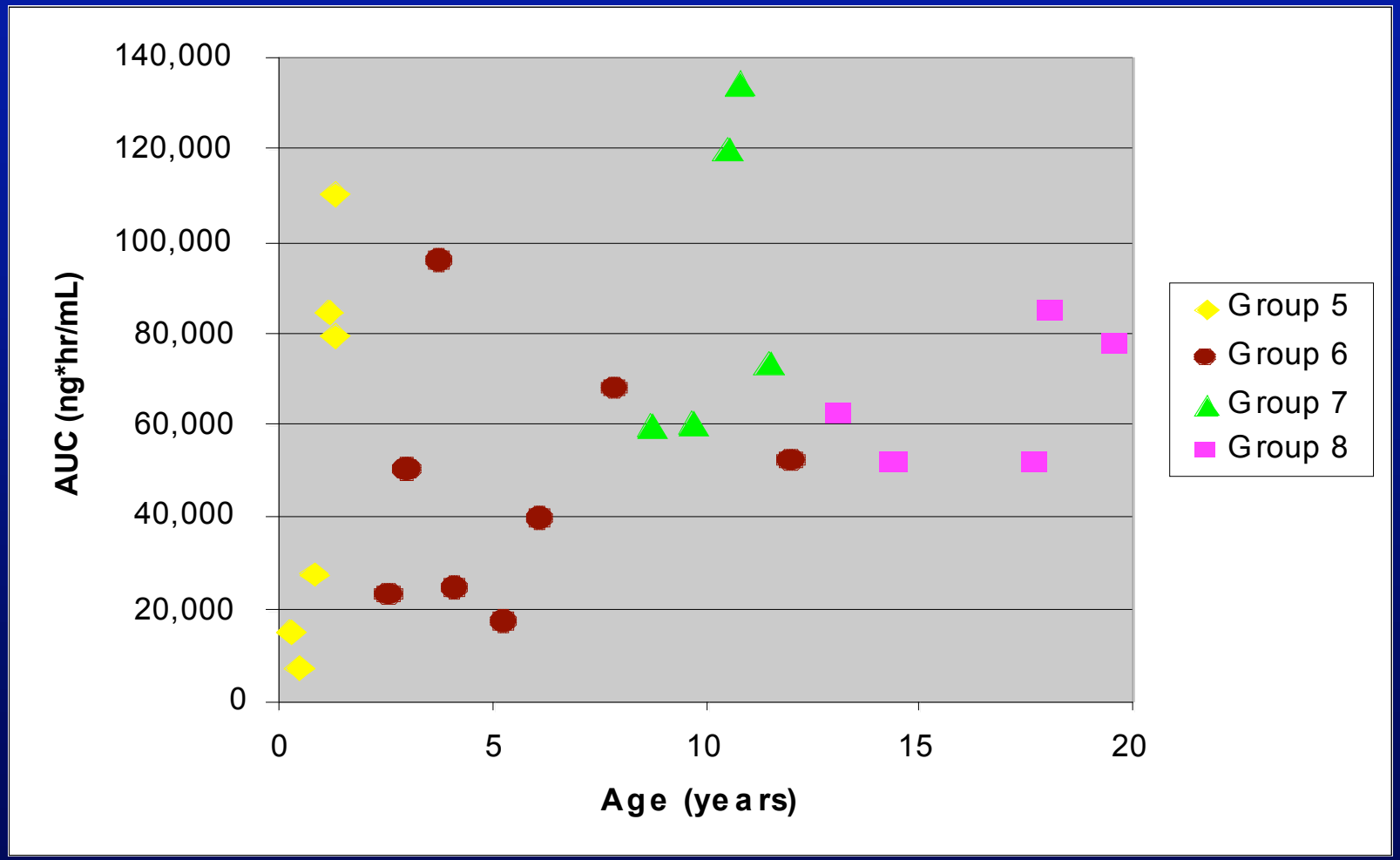
- time lag between prescription & administration of new dose

# Pediatric Challenges

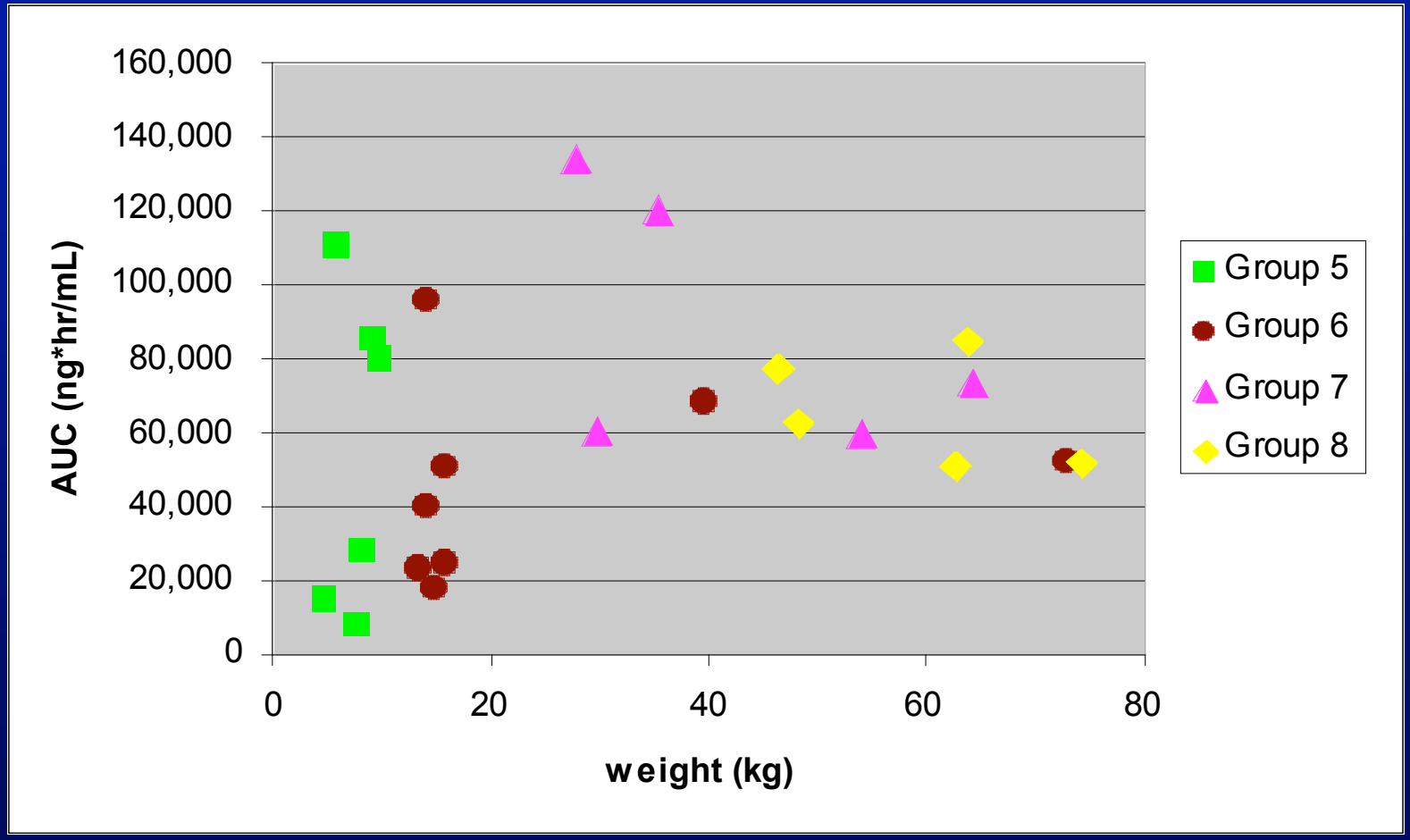
- Children are not small adults.
- Dosing recommendations cannot be developed for an “average” child
  - –by age or weight
  - –ignores maturational differences in PK
- The challenges of developing an acceptable pediatric formulation are significant
  - –bioavailability in adults ≠ bioavailability in children

J Kiser, U Colorado

# ATV AUC by Age



# ATV AUC by Weight



# Future Directions

- Thoughtful consideration of pediatric maturational changes in PK during study design and how they are ultimately incorporated into pediatric dosing guidelines
- Studies of formulation bioavailability in children
- Therapeutic drug monitoring of ARV drugs in this population

# Regulatory Issues

# South Africa MCC: Approval for pediatric use

If indications for use are similar to those in adults:

- Efficacy can be extrapolated from adequate and well-controlled studies in adults if safety, and PK-PD data in children are available
- Extrapolation from one age group to another age group where appropriate may also be considered

# Bioequivalence Studies

**Demonstration of bioequivalence may be sufficient if component drugs are already approved**

- Approved drugs must be very well characterised
- There must be extensive clinical experience of combined use
- There must be clear evidence of advantage for the combination

# Clinical Safety/Efficacy Studies

**Clinical studies of the FDC may be required if:**

- there is limited clinical experience with the component drugs
- the proposed benefit of the combination is unclear or unknown
- the safety of the combination is unknown (bridging toxicity studies may also be required)
- the combination includes a new molecular entity (non-clinical pharmacology/toxicology also required)

# Bioequivalence Testing

- Bioequivalence study
  - Appropriate design
  - Criteria for selection
  - Choice of comparator/reference products
- Pharmacokinetic parameters
  - Importance of AUC, $C_{max}$, $C_{min}$, $t_{1/2}$ for each API with respect to daily dosing regimen (QD, BID, TID)
- Effect of food on PK profile
- Characteristics of APIs (solubility, permeability) in relation to formulation (reduced particle size, stabilized amorphous systems, or solutions)
  - APIs typically dosed in an immediate release formulation, may show altered PK profiles if incorporated into a modified release formulation (altered bioavailability)
- *In vivo* interactions between API's or formulation excipients may alter PK profile

# Post-Approval Issues

- Importance of post -marketing surveillance and post-marketing studies to detect and evaluate new patient safety and efficacy data
  - Pharmacovigilance
  - Requirements for monitoring and reporting
- Specific FDC -related issues:
  - Allergy to a component in the FDC
  - Impact on emergence of drug resistant strains

# Pediatric Formulation Approval

- Formal indication for use in pediatric population would require a Phase III Study.

However,

- General HIV/AIDS indication with pediatric dosing:
  - Basic indication of efficacy
  - Some indication there is no difference in safety profile
  - Pharmacokinetic data
  - Acceptable pre -clinical profile

# Fixed Dose Combination (FDC) Product

1) New FDC is generic bioequivalent to existing FDC
   - Bioequivalence data only
2) New FDC developed by combining individual components from a well studied multi-drug regimen
   - BE Study comparing new FDC to individual components
   - Supporting data (literature or previously filed)

# Fixed Dose Combination (FDC) Product

3) Individual components that are well studied individually but the multi -drug regimen is not well studied or used in a novel dosing regimen
   - Bridging toxicology studies (minimum)
   - Appropriate PK and pharmacodynamic studies
   - Clinical study(s) to support the combination of active ingredients or the novel dosing regimen
4) New Chemical entity
   - Full pre-clinical and clinical package

# U.S. legislation affecting pediatric drug development

- Best Pharmaceuticals for Children Act
  - Extends 6 months patent protection to companies that perform requested pediatric studies (voluntary)
- Pediatric Research Equity Act (2003)
  - Any drug that may provide benefit to children must be studied in children (mandatory)

# Development of pediatric formulations - Key issues

- Stability of formulation (temperature, reliable drug release)
- Acceptable palatability
- Ability to achieve target exposure associated with efficacy in adults
- Convenience

# Extra problems - use of adult formulations in children

- If splitting tablets - ensure that procedure can be performed reliably by target population
- If crushing tablets or opening capsules - may need PK data to support that route
- If using adult FDC - must ensure each component provided in recommended dose for age range being treated

# Evaluating pediatric formulations – new drugs

- Pharmacokinetic evaluation
  - Determine how to achieve target exposure found to be safe and effective
  - Should include all age groups (enough patients sampled to identify variability)
  - Initial dose estimate - consider developmental changes in absorption, metabolism, excretion
- Monitor tolerability and safety
- Assess activity in pediatric age groups

# Evaluating pediatric formulations – "generics"

Evaluate bioequivalence

- Single product - compare generic to reference drug (innovator)
  - For FDC product - compare generic FDC to individual reference drugs taken together
  - Preferred study design is randomized, single-dose, 2-way cross-over
- Monitor tolerability and safety

# Evaluating pediatric formulations – "generics"

- Considerations
  - Bioequivalence studies need not be done in children
  - If comparing 2 oral solutions no BE study required, if comparing formulations other than solutions BE study required
  - Evaluating solid or suspension formulations – dissolution testing required (assurance of reproducible drug release)

# Application of pediatric initiatives to FDC development

- Fixed dose combination products
  - Want to encourage development of FDCs appropriate for pediatric patients
  - Some FDCs may not be appropriate for all ages (dose, proportion of component drugs)
  - Need to consider on a case -by-case basis

# EU Regulatory considerations

Draft European Regulation on Paediatric Medicinal Products

- Ongoing discussion at the EU Parliament and the Council
- Expected by end 2006
- Implementation 2007

# CHMP Guideline on the clinical development for anti-HIV medicinal products

## Children

- Development of a suitable pharmaceutical formulation for children normally expected to take place early.
- Recommendation on data to be provided to support use in children

*Currently released for 3 months consultation*

# CHMP PAEDIATRIC WORKING PARTY

- Assessment of paediatric needs with help of PENTA
- For HIV medicinal products already authorised in EU, conclusions sent to the companies
- Still under discussion

# Research Challenges

- Availability of drugs for research in resource-limited settings
  - what is allowed in US sponsored research programs
    - Purchase drugs? If so, then which ones?
    - Responsibility for rolling over into treatment programs once clinical research phase is completed
    - Ethical and cultural appropriateness concerns
    - Lack of understanding of what the needs are (e.g. liquid vs solid formulations)
- Need ongoing research for better treatments while acknowledging the urgency of treatment need and public health approach

# Treatment research issues

- Need better treatments for children with co-morbidities
  - E.g. HIV/TB co-infection
  - South Africa uses Kaletra in first line vs other countries using nevirapine/efavirenz combinations in first line

# Program Challenges

- Requirement for different types of approval for treatment roll-out programs
  - PEPFAR: US FDA approval
  - Global Fund: approval by a stringent regulatory body
  - WHO Pre-Qualification program
- Integration of operational research questions into treatment programs

# At the end of the day….

- Confusion as to what exactly is required to have pediatric “formulations” approved still exists
- Clarification urgently needed

## Recommendations

- Consider age-bracket approval as necessary in situations where data is not available for all age groups
- Establish a working group to work out the details and mechanisms to have drugs approved more rapidly for pediatric use through the various mechanisms
- Establish a working group to simplify dosing schedules, integrate new data as it becomes available
  - Consistent approach to dosing within clinical trials and dosing recommendations
- Work on harmonization of regulatory requirements
- Support research in maturation issues as they relate to PK in children
- Palatability
  - Work with children's food industry – experts in science of providing and marketing culturally appropriate "attractive" food items

# Recommendations

- Develop more expertise in pediatric clinical pharmacology
- Linking of pediatric research and treatment programs to MTCT programs
- Linking of research networks to maximize operational capacity and information exchange
  - E.g. EGPAF MTCT sites, MSF network of pediatrics in treatment programs, PENTA, PACTG
- Advocacy for pediatric issues (dosing, treatment, monitoring, etc, etc, is needed

# Forum plans

- Working group on pediatric treatment monitoring and diagnostic issues
- Continue working in the area of pediatric formulations and treatment in collaboration with -- and complementing programs of -- EGPAF, WHO and other organizations
  - Contact us if interested in joining working groups
- All slides of workshop will be available on website
  - www.hivforum.org
- Look for meeting report!